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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,370	10/03/2001	Randall K. Holmes	33,383-00	8568

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,370	HOLMES ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/29/05.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11,13-17,28-37 and 39-44 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11,13-17,28-37 and 39-44 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13-17, 28-37,39-44 are pending.
Claims 12, 18-27 and 38 have been canceled; new claim 44 has been added.
Claim 1 and all claims dependent therefrom have been amended; Claims 15 and 16, 29, 41-43, also have been amended.

Allowable Subject Matter

1. Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Additionally, claim 29 is rejected under 35 USC 112, second paragraph set forth below. Obviating the rejection under 35 USC 112, second paragraph could define allowable subject matter.
2. Claims 3 and 44 define over the prior art of record and are therefore allowed, but are rejected under 35 USC 112, second paragraph set forth below. Obviating the rejection under 35 USC 112, second paragraph could define allowable subject matter.

Rejections Maintained

3. Claims 1-2, 4, 6-8,11, 13-17, 28, 30,32-34, 37, 39-43 rejected under 35 U.S.C. 102(b) as being anticipated by WO95/17211 (as evidenced by sequence for cholera toxin and E.coli heat labile enterotoxin provided by Zhang et al (1995, page 564, Figure 1)), is maintained for reasons of record and responses to Remarks set forth below.
4. Claims 1, 2, 13 rejected under 35 U.S.C. 102(b) as being anticipated by Glineur et al (1994) is maintained for reasons of record and responses to Remarks set forth below.

Response to Declaration/Amendment

5. In response to Appellant's Appeal Brief and Declaration submitted After Final, the finality of the rejection of the last Office action is herein withdrawn for the purpose of setting forth clarifying statements and grounds of rejection with respect to improper incorporation of Essential Material; therefore, the finality of that action is withdrawn.

Response to Declaration by Ms. Mary E. Bak

6. The Declaration of Ms. Mary E. Bak states that the incorporation of WO93/13202 in light of evidence provided by Mekalanos et al 1983 is a "properly incorporated by reference".

7. It is the position of the examiner that subject matter contained within the Specification of WO93/13202 has been incorporated into the instant Specification and claims, and therefore encompasses Essential Material.

- SEQ ID NO 1 is taken from WO93/13202, which adds an amino acid sequence for which Applicant does not have original descriptive support. Applicant's original sequence listing only set forth nucleic acid primers (see attachment labeled "original sequence listing") and No amino acid sequences. In light of the Declaration of Ms. Bak not properly making statements required for proper incorporation of essential subject matter into the Specification, SEQ ID NO 1 is New Matter.
- Instant claims 15 and 16 recite a combination of claim limitations supported by narrative found on page 38 of the instant Specification and are defined in WO93/13202. The narrative found in the instant Specification is "The antigenic compositions of this invention also comprise CT-CRM containing at least one additional mutation at a position other than at amino acid residue 29. International Application WO93/13202 (36), which is herein incorporated by reference describes a series of mutations in the A subunit which serve to reduce the toxicity of the cholera holotoxin." The incorporation of **essential material** in the specification by reference to an unpublished U.S. application, *foreign application* or patent, or *to a publication is improper*. Applicant is required to amend the disclosure to include the material

incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. **The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter.** 37 CFR 1.57(f). The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material **consists of the same material incorporated by reference in the referencing application.** In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167(CCPA 1973).

- The attempt to incorporate subject matter into this application by reference to WO93/13202 and Mekalanos et al (1983) is ineffective because the instantly submitted Declaration does not set forth the required statement "the amendatory material consists of the same material incorporated by reference in the referencing application."
- The new rules for incorporation by reference do not apply in light of Applicant's filing date falling prior to September 21, 2004 and therefore falls under the old rules which requires the submission of an effective Declaration which includes the above bolded statement.
- Upon consideration of the phrase "at least one additional mutation" found in the instant Specification at page 38, paragraph 2 (page 38 attachment provided herewith),

defined by the disclosure of WO93/13202, the examiner found at page 7, lines 5-24 of WO93', especially lines 19-24 the definition of "substitution " to include deletions of amino acids (WO93', page 7, attachment provided herewith). The exact narrative follows:

"The substitution may involve *deletion of an amino acid* altogether provided that the mutant retains the necessary immunogenic properties and exhibits a substantially reduced toxicity (emphasis added) ". Therefore a substitution of an amino acid at a specific location may be achieved through deletion of an amino acid residue. This definition has been incorporated by reference to the WO93' reference, especially in light of the fact that claims 15 and 16 recite the mutations defined in WO93'.

- In light of the definition incorporated by reference in WO93' for the phrase "at least one additional mutation" providing for and encompassing deletions of amino acids, as long as the resultant holotoxin retains its desired biological activity, the scope of the instantly claimed invention includes deletions of amino acids within the A-subunit of cholera toxin, the *deletion resulting in a substitution of an amino acid* at the residue position at which the deletion mutagenesis was carried out. This definition of substitution was incorporated by reference at page 38 of the instant Specification, lines 11, and 28-29.
- The instant Specification has also defined additional species within the scope of the claims to include mutants of the chimeric cholera CRM which were produced from two different strains of Vibrio cholera (described on page 35 of the instant Specification (attachment provided herewith)). The A subunit amino acid sequence

was obtained from Vibrio cholerae strain 569B and was linked to the amino acid sequence for the B-subunit from Vibrio cholera strain 2125. The resultant polypeptide evidenced several changes in the overall amino acid sequence "Cross alignment of these genes indicated seven base substitutions between the two ctxB genes and a single base change between the ctxA genes. Several of these base substitutions led to amino acid changes in the mature subunits." What these changes were are not described in the Instant Specification by amino acid residue number.

- At pages 44-45 of the Instant Specification, a deletion mutant was produced through removing the native signal sequence of cholera toxin, and the signal sequence replaced with the signal sequence of LT (LTIIb-B leader (attachment provided herewith)), which resulted in the addition of amino acids to the overall sequence. The specific narrative is:

" The regions encoding ctxA and ctxB signal sequences were replaced with the signal sequence encoding region of E.coli LT (LTIIb-B leader) in order to promote secretion of CT-CRM $_{E29H}$. The plasmid pIIB29H was then modified in an attempt to increase expression of CT-CRM $_{E29H}$. The resulting plasmid, designated pPX2492, contained synthetic Shine Dalgaro sequences upstream of each of ctxA and ctxB. The two genes are genetically separated in pPX2492, unlike in V. cholerae, where the genes overlap. The two genes also have the LTIIb-B leader sequence upstream of each."

The leader sequence of LTIIb-B of E.coli is a 23 amino acid sequence while the leader sequence of cholera toxin is generally 18 amino acids. Both the A subunit and the B subunit comprise 5 additional amino acids to the overall size of the polypeptide.

- An additional embodiment is set forth at page 108, with ctxA and ctxB from strain 569B but has the LTIIb-B leader sequence (page 108, attachment provided herewith). The encoded amino acid sequence is described to be

encoded by a "similar fragment", but what the amino acid sequence is, is not structurally defined, but is only similar. The size, exact amino acid sequence and where changes exist is only described by the relative term "similar".

- What is claimed is a mutant polypeptide, the size of which is not claimed by a reference amino acid sequence identifier, and the only reference point for the claimed mutant is that of the wild-type holotoxin, but what is now claimed is a mutant. The specification defines mutants with substitutions, deletions and additions to the overall size of the claimed mutant cholera toxin which need only evidence adjuvanting activity.

In light of the discussion above, the rejection of all of the claims under 35 USC 112, second paragraph is herein reinstated, and new grounds of rejection/objection under 35 USC 112, first paragraph (New Matter) will be set forth below.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-11, 13-17, 28-37, 39-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For the reasons set forth above under the header "Response to Declaration" and the fact that the cholera toxin subunit A is known to have sequence variation (see Swiss Prot Accession numbers Q8vL16, Q81356, and P01555) what the meets and bounds of the claimed mutant cholera toxin are, are unclear. Resolution of improper incorporation by reference to critical subject matter could be obviated through submission of an effective Declaration and insertion of a reference sequence into the independent claims could obviate this rejection. It is not clear whether the A-subunit number starts with or without the signal sequence, as the type of A-subunit could be in the pro-toxin form or in the form where the signal sequence has been cleaved; based upon these two situations, the numbering from the N-terminal of the protein antigen would result in a different position for substitution of the amino acid.

Specification

11. The amendment filed July 12, 2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO 1. The amino acid sequence was improperly incorporated by reference to International Application WO93/13202. No original descriptive support in the instant Specification could be for the amino acid sequence of SEQ ID NO 1. Applicant in claims 15 and 16 claims the embodiments disclosed in WO93' in

combination with Applicant's mutation set forth in at least claim 1. Therefore the Specification has been amended to recite narrative that is New Matter. Applicant is required to cancel the new matter in the reply to this Office Action or submit an effective Declaration for the proper incorporation by reference of essential subject matter.

Prior Art Rejections Maintained

The prior art rejections maintained will be briefly discussed in light of the fact that the WO93' definition of "substitution" includes deletions of amino acids (see page 7, lines 5-24, WO93) and the narrative of WO93' has been incorporated by reference into the instant Specification. WO95/17211 and Glineur et al both produced mutant cholera holotoxins with the amino acid at position 29 replaced through deletion of an amino acid. The replacement of the amino acid at position 29 resulted in a tyrosine existing at position 29. Applicant's claims have only excluded aspartic acid from existing at position 29, and therefore the mutant cholera holotoxins with a tyrosine at position 29 is within the scope of Applicant's invention. The overall size of the claimed mutant cholera holotoxin is not required to be any overall specific size or sequence and is only functionally defined as evidencing adjuvanting activity. The prior art rejections are maintained for reasons of record.

Conclusion

12. This is a non-final action.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
November 8, 2005

NITA MINNIFIELD
PRIMARY EXAMINER
11-9-05